REMARKS

Claims 11-13 and 20-38 are pending in the present application.

The rejection of Claims 11-13 and 20-38 under 35 U.S.C. §103(a) over Abraham (with support from Clarke et al and Macheix et al) in view of Hsu as supported by McGraw-Hill and Yokozawa et al is respectfully traversed.

The present invention relates to a combination of ferulic acid (or an ester thereof), and caffeic acid and/or chlorogenic acid, which exerts prompt blood pressure lowering effects and, by prolonged administration, suppresses rises in blood pressure. This combination of ingredients also has reduced side effects such as bradycardia.

Representative of this invention is the sole independent claim (Claim 11) in this application:

> A process for preventing or treating hypertension or high blood pressure comprising: administering an effective dose of a composition comprising (a) ferulic acid or an ester thereof, or a pharmaceutically acceptable salt thereof, and (b) a component selected from caffeic acid, chlorogenic acid, caffeic acid and chlorogenic acid, and pharmaceutically acceptable salts thereof, to a subject in need thereof, wherein systolic blood pressure, diastolic blood pressure, or both is reduced.

Applicants previously submitted that the combination of references (a) fail to disclose or suggest the co-administration of ferulic acid with caffeic acid and/or chlorogenic acid to treat or prevent hypertension or high blood pressure, and (b) fail to realize the benefits flowing from the combined use of components.

In making this rejection, the Examiner points to composition code (D) appearing in Table 1 of Abraham et al as containing ferulic acid, caffeic acid, and chlorogenic acid. Further, the Examiner points to Table 2 of Abraham et al and asserts that the supplement identified as composition code (D) is added to coffee, composition code (C). Be that as it may, the Examiner acknowledges that Abraham et al fail to disclose or suggest the

administration of such a composition for the treatment or prevention of hypertension. Notably, Abraham et al is directed to the anti-genotoxic (Genotoxic substances are a type of carcinogen, specifically those capable of causing genetic mutation and of contributing to the development of tumors) effect of certain dietary constituents.

In an attempt to compensate for this deficiency, the Examiner asserts that Hsu discloses treating hypertension using the herb Crataegus, which contains the active ingredients chlorogenic acid and caffeic acid. The Examiner further references Yokozawa et al as disclosing that caffeic acid and its derivatives are effective for treating hypertension.

Although Abraham et al disclose the co-administration of ferulic acid *with* caffeic acid and/or chlorogenic acid (the compound or the genus) to produce an anti-genotoxic effect, there is no disclosure in any of these references for the co-administration of ferulic acid with anything to prevent or treat hypertension or high blood pressure.

The Examiner alleges that "it would have been obvious to someone skilled in the art, knowing the teachings of Hsu, to treat hypertension using the composition of Abraham. Hsu provides the motivation by plainly stating that caffeic acid and chlorogenic acid are know treatments for hypertension. The reasonable expectation of success is provided by Hsu who states that Crataegus with its active ingredients of chlorogenic acid and caffeic acid are used to treat hypertension." Applicants respectfully submit that this allegation by the Examiner is an oversimplification and inaccurate representation of the disclosure of Hsu.

In contrast to the Examiner's alleged disclosure by Hsu, at column 2, lines 55-61, Hsu actually disclose:

> Crataegus is generally known in the West as hawthorn (Crataegus oxyacantha). Crataegi are usually encountered as a tree or a bush, and the normally used medicinal parts are the flowers and the fruit. The active principles are reported to be chlorogenic acid, caffeic acid, citric acid, crataegolic acid, malinic acid, ursolic acid. Crataegus is used to treat hypercholesterolemia, angina pectoris, and hypertension.

From the foregoing, it is clear that Hsu do not disclose that chlorogenic acid and caffeic acid are sufficient to treat hypertension as the Examiner alleges. What Hsu actually discloses is that "*Crataegus* is used to treat... hypertension" and that Crataegus contains 6 known active ingredients: chlorogenic acid, caffeic acid, citric acid, crataegolic acid, malinic acid, and ursolic acid. From this disclosure, it can only be concluded that when all six of these *identified* active ingredients and any number of unidentified active ingredients and other ingredients present in Crataegus are present can hypertension be treated. This disclosure does not provide any motivation to co-administer chlorogenic acid and/or caffeic acid with ferulic acid as the Examiner contends. Further, it is again submitted that no evidence has been offered as to the effect of ferulic acid on hypertension. Abraham only relates to the administration of the compositions appearing in Table 1 to determine their anti-genotoxic effects. At no point does the art of record disclose the co-administration of ferulic acid *with* caffeic acid and/or chlorogenic acid (the compound or the genus) to prevent or treat hypertension or high blood pressure.

Therefore, with respect to the first difference, there is simply no basis to support the motivation allegation by the Examiner. This deficiency in the art of record is important and evidence for the same is provided in the Examples of the present application (second difference). Specifically, the experimental data set forth in Table 1 (page 15; see below) of the present application, shows the clear advantages of co-administration of ferulic acid with caffeic acid and/or chlorogenic acid.

The Examiner is reminded that as set forth in MPEP §716.02(a) "greater than expected results are evidence of nonobviousness." Evidence of a greater than expected result may also be shown by demonstrating an effect which is greater than the sum of each of the effects taken separately (i.e., demonstrating "synergism"). *Merck & Co. Inc. v. Biocraft*

Laboratories Inc., 874 F.2d 804, 10 USPQ2d 1843 (Fed. Cir.), *cert. denied*, 493 U.S. 975 (1989).

Table 1

	Systolic blood pressure (changing ratio %)		
		after 10 minutes	After 1 hour
Control plot	saline	-1.6 ± 0.6	-1.9 ± 1.4
Test plot 1	Caffeic acid (CA)	-4.1 ± 2.1	-10.2 ± 0.5 ***
Test plot 2	Chlorogenic acid (CHA)	-3.2 ± 2.6	-7.2 ± 1.7 *
Test plot 3	Ferulic acid (FA)	-7.8 ± 0.8 ***	0.7 ± 2.6
Test plot 4	CA + FA	-10.4 ± 1.8 ***	-11.3 ± 1.3 ***
Test plot 5	CHA + FA	-9.6 ± 2.2 ***	-10.9 ± 0.8 ***
Test plot 6	CA + CHA +FA	-11.1 ± 1.9 ***	-13.6 ± 3.4 ***

*, ***; A significance level was 5% or less and 0.1% or less, respectively relative to the control group, meaning existence of a significant difference.

By comparing Test Plots 4-6 to Test Plots 1-3 and looking at the 1 hour point it is clear that the co-administration of ferulic acid with caffeic acid and/or chlorogenic acid is clearly greater than the additive values of the individual administration of these compounds, thus providing evidence of synergism.

In the outstanding Office Action, the Examiner disregards the argument of synergism alleging that the data above do not support a conclusion of synergism for two reasons:

1) the effects are additive at 10 minutes; and

2) taking into account the error intervals, the effects "are simply the sum of their individual effects."

The first criticism is without merit as "Evidence of unobvious or unexpected advantageous properties, such as superiority in a property the claimed compound shares with

the prior art, can rebut *prima facie* obviousness. "Evidence that a compound is unexpectedly superior in one of a spectrum of common properties . . . can be enough to rebut a *prima facie* case of obviousness." No set number of examples of superiority is required. *In re Chupp*, 816 F.2d 643, 646, 2 USPQ2d 1437, 1439 (Fed. Cir. 1987)" Thus, the effects demonstrated at the 1 hour time point are sufficient evidence of superiority, regardless of what is shown after 10 minutes.

As for the second criticism, the Examiner appears to fixate on the standard deviations for the values reported in the Table. However, Applicants submit that this criticism overlooks the statistical significance reported in the Table. Applicants submit that the data set forth in the Table do support a conclusion of synergism. This is especially apparent when comparing Test Plots 4 and 5 to Test Plots 1-3 and looking at the 1 hour point.

In view of the foregoing, Applicants request withdrawal of this ground of rejection.

The obviousness type-double patenting rejection of Claims 11-13 and 20-38 over Claims 1-11 of U.S. Patent No. 6,310,100 in view of Abraham as supported by Hsu and Yokozawa et al is respectfully traversed.

Applicants submit that this ground of rejection is without merit as the claims of U.S. Patent No. 6,310,100 fail to include ferulic acid in addition to caffeic acid and/or chlorogenic acid, which is required in the claimed invention. Abraham, Hsu, and Yokozawa et al are summarized above, as are their combined disclosures.

The Examiner contends that the generic phrase in Claim 5 of US 6,310,100 "and at least one other anti-hypertensive compound", supported by Abraham, Hsu, and Yokozawa et al, would embrace caffeic acid and chlorogenic acid as "anti-hypertensive compounds". Even if this were the case, the present invention would represent a selection invention and the prima facie case of obviousness is rebutted by the data set forth in the present specification.

Specifically, for the reasons set forth above, Applicants submit that the data set forth in Table 1 clearly show the substantial advantages flowing from the claimed combination as compared to compositions in which only ferulic acid is present (i.e., U.S. Patent No. 6,310,100). As such, Applicants submit that the claims of the present application are pantentably distinct from the claims of U.S. Patent No. 6,310,100.

Accordingly, withdrawal of this ground of rejection is requested.

Finally, Applicants request that the provisional obviousness-type double patenting rejection of Claims 11-13 and 20-38 over Claims 2-6, 8, 11-16, and 20-29 of U.S. 10/826,289 and over Claims 1-19 of U.S. 09/922,694 be held in abeyance until allowable subject matter is identified in each application. If necessary, a terminal disclaimer will be filed at that time. Until such a time, Applicants make no statement with respect to the propriety of this ground of rejection.

Applicants submit that the present application is now in condition for allowance. Early notification of such action is earnestly solicited.

Respectfully submitted,

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